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[54] **PROMOTION OF WOUND HEALING BY CHEMICALLY-MODIFIED TETRACYCLINES**

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[58] **Field of Search** 514/152

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,823,212	7/1974	Chvapil .	
4,016,877	4/1977	Cruz, Jr. et al. .	
4,130,555	12/1978	Ohtsuka et al. .	
4,294,241	10/1981	Miyata .	
4,407,787	10/1983	Stemberger .	
4,412,947	11/1983	Cioca .	
4,440,680	4/1984	Cioca .	
4,578,067	3/1986	Cruz, Jr. .	
4,666,897	5/1987	Golub et al. .	
4,704,383	11/1987	McNamara et al.	514/152
4,813,942	3/1989	Alvarez .	
4,834,734	5/1989	Morganti .	
4,837,024	6/1989	Michaeli .	
4,841,962	6/1989	Berg et al. .	
4,925,833	5/1990	McNamara et al. .	
4,935,412	6/1990	McNamara et al.	514/152
4,950,483	8/1990	Ksander et al. .	
4,969,912	11/1990	Kelman et al. .	
5,008,283	4/1991	Blackburn, Jr et al.	514/414
5,024,841	6/1991	Chu et al. .	
5,081,106	1/1992	Bentley et al. .	
5,110,604	5/1992	Chu et al. .	
5,156,601	10/1992	Lorenz et al. .	
5,196,196	3/1993	Scott et al. .	
5,227,168	7/1993	Chvapil et al. .	
5,240,958	8/1993	Campion et al.	514/445
5,258,371	11/1993	Golub et al.	514/152
5,308,839	5/1994	Golub et al.	514/152
5,459,135	10/1995	Golub et al.	514/152
5,532,227	7/1996	Golub et al.	514/152

FOREIGN PATENT DOCUMENTS

1767900A	9/1971	Germany .
91/15506	10/1991	WIPO .

OTHER PUBLICATIONS

Chang et al., "Local and Systemic Factors in Periodontal Disease Increase Matrix–Degrading Enzyme Activities in Rat Gingiva: Effect of Micocycline Therapy", Research Communications in Molecular Pathology and Pharmacology, 91(3):303–318 (1996).

Clark, "Cutaneous Wound Repair," Dermal Macromolecules and Their Metabolism, 576–601 (1990).

Clark, RAF, "Biology of Dermal Wound Repair," Dermatol. Clinics 11(4):647–666 (1993).

Golub et al., "Further Evidence That Tetracyclines Inhibit Collagenase Activity in Human Crevicular Fluid and from Other Mammalian Sources," J. Periodontal Res. 20:12–23 (1985).

Golub et al., "Treating Periodontal Diseases by Blocking Tissue–Destructive Enzymes," J.A.D.A. 125:163–171 (1994).

Golub et al., "Tetracyclines Inhibit Connective Tissue Breakdown: New Therapeutic Implications for an Old Family of Drugs," Critical Reviews in Oral Biology and Medicine, 2(2):297–322 (1991).

Inoue et al., "Collagenase Expression Is Rapidy Induced in Wound–Edge Keratinocytes After Acute Injury in Human Skin, Persists During Healing, and Stops at Re–Epithelialization," The Journal of Investigative Dermatology, 104(4):479–483 (1995).

Mitscher, LA, The Chemistry of the Tetracycline Antibiotics, Ch. 6, Marcel Dekker, New York (1978).

Ramamurthy NS et al., "The Effect of Diabetes on Lysyl Oxidase Activity and Extractability of Newly Synthesized Collagen In Rat Gingiva and Skin," Gerodontology, 2:15–19 (1983).

Ramamurthy NS et al., "Endotoxin Induces MMP Mediated Bone Loss In Rat Periodontium: Inhibition of Matrix Metalloproteinases by CMT's," Journal of Dental Research, 75:105 (1996).

Ryan et al., "Matrix Metalloproteinases and Their Inhibition In Periodontal Treatment," Current Opinion in Periodontology, 3:85–96 (1996).

Stegemann, H, "Mikrobestimmung von Hydroxyprolin mit Chloramin–T und p–Dimethylaminobenzaldehyd" (A Microcolorimetric Assay for Hydroxyproline), Hoppe–Seylers Z Physiol. Chem. 311:41–45 (1958) (with English abstract).

Schneir M, N Ramamurthy, and L Golub, "Minocycline–Treatment of Diabetic Rats Normalizes Skin Collagen Production and Mass: Possible Causative Mechanisms," Matrix 10:112–123 (1990).

Zhang et al., "Chemically Modified Tetracycline (CMT–6) Applied Topically Enhances Diabetic Wound Healing," Journal of Dental Research, 75:108 (1996).

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[57] **ABSTRACT**

A method for improving the healing response of epithelialized tissue (e.g., skin, mucosae) to acute traumatic injury is disclosed. The method includes employing a tetracycline compound, having substantially no antibacterial activity, to improve the capacity of the epithelialized tissue to heal acute wounds. Specifically, the method involves increasing the rate of collagen accumulation of the healing epithelialized tissue above that associated with wound healing in the individual. The method decreases proteolytic activity in the epithelialized tissue by means of the tetracycline compound, most commonly decreasing collagenolytic activity and/or decreasing gelatinolytic activity. Collagenase and gelatinase activity have been shown to be decreased by the method of the invention. Preferably, the method is employed to improve the wound healing capacity of human or animal subjects in whom such capacity is impaired. Also, the non-antibiotic tetracycline is preferably administered topically at the site of the wound.

9 Claims, 2 Drawing Sheets